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(54) USE OF A COMPOSITION COMPRISING FORMOTEROL AND BUDESONIDE FOR THE PREVENTION OR TREATMENT OF AN ACUTE CONDITION OF ASTHMA

VERWENDUNG EINER ZUSAMMENSETZUNG WELCHE FORMOTEROL UND BUDESONIDE ENTHÄLT, ZUR VERHINDERUNG ODER BEHANDLUNG EINES AKUTEN ASTMAZUSTANDES

UTILISATION D'UNE COMPOSITION COMPRENANT DU FORMOTEROL ET DU BUDESONIDE POUR LA PREVENTION OU LE TRAITEMENT D'UN ETAT AIGU D'ASTHME

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(73) Proprietor: **AstraZeneca AB**
151 85 Södertälje (SE)

(72) Inventor: **EKSTRÖM, Tommy**
S-221 87 Lund (SE)

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WO-A1-93/11773

- **THE NEW ENGLAND JOURNAL OF MEDICINE ROMAIN A.PAUWELS ET AL: 'Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma' vol. 337, no. 20, November 1997, pages 1405 - 1411, XP002919900**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to the use of a composition comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma characterised in that the use is for symptomatic relief, when needed, in addition to treating chronic asthma on a regular basis.

BACKGROUND OF THE INVENTION

[0002] Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms may be controlled by β_2-adrenoceptor agonists such as terbutaline, salbutamol, formoterol and salmeterol. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate, fluticasone propionate, mometasone furoate and budesonide.

[0003] In spite of modem maintenance treatment too many asthmatic patients are undertreated for a number of reasons with a negative impact on their quality of life. Too complicated therapy with different medications and devices may lead to misunderstanding and communication problems between patient and doctor. Poor compliance is a common phenomenon. Improved patient education may partly counteract this, but does not completely solve the problem. A new and more simple approach to asthma treatment could thus be of tremendous help for many patients suffering from respiratory disease, particularly asthma, The combination of budesonide and formoterol in the same device as suggested in PCT applications WO 93/11773 and WO 98/15280 (both to Astra AB of Sweden) offers a favorable pathway to improve today's asthma management with an excellent safety profile. However, although having an adequate regular, e.g. bid, treatment with such a combination, many patients will now and then run into acute situations with a higher frequency and severity of exacerbations, when additional medication is needed. Such an additional medication is often a β_2-adrenoceptor agonist with fast onset, normally terbutaline or salbutamol. A second medicament is thus needed, and this can negatively affect the overall compliance of the patient. There is thus need for a neat way of handling maintenance treatment together with the treatment of acute situations.

SUMMARY OF THE INVENTION

[0004] It is an object of the present invention to provide use of a suitable composition for the manufacture of a medicament for the treatment of acute episodes of asthma as a complement to maintenance treatment.

[0005] More specifically, according to the invention there is provided the use of a composition comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma characterised in that the use is for symptomatic relief, when needed, in addition to treating chronic asthma on a regular basis.

[0006] Use of the present composition, when needed, relates to use of said composition during one or more of the following conditions:

i) an acute condition of asthma, i.e. acute asthma attacks,
ii) intermittent asthma and/or
iii) short periods (episodes) of acute attacks of bronchospasms in chronic asthma.

[0007] Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g. during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient.

[0008] It lies within the scope of the present invention, to use the compositions comprising active compounds (a) and (b) for treating acute conditions of asthma, intermittent asthma and episodes in chronic asthma, in addition to treating chronic asthma on a regular basis, with the same active compounds (a) and (b) or one or more different active compounds, preferably selected from short-acting β-agonists, long-acting β-agonists and glucocorticosteroids.

[0009] We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

[0010] According to the present invention it has surprisingly been found that the medicament can be administered when needed to a patient with an acute attack of asthma.

[0011] The recommended dose regimen described in the prior art as disclosed above is twice a day. This dose recommendation was a result of a concern not to have

too high an administration of the active compounds. However, in the present invention it has been found that it is possible for the patient to administer this mixture as often as needed.

[0012] The combination of formoterol and budesonide can be used as a rescue medication. Worsening of symptoms can be counteracted by incremental use of the combination for symptom relief, e.g. during exacerbations with the additional steroid component coming in as early as possible to suppress the enhanced airway inflammation. The long duration of formoterol will reduce the risk of too frequent dosing. When taking the combination budesonide/formoterol when needed the severity of exacerbations can be reduced. The as needed use (Pro Re Nata, PRN) will also minimize the difficulty of predicting which patients will be controlled on a low dose of inhaled steroid rather than increasing the steroid dose before adding a long-acting β_2-agonist. Under-treatment with inhaled glucocorticosteroids following a too low maintenance dose will be more or less "self-corrected" by the rescue usage according to the present invention. The PRN use of the combination will always give some beneficial anti-inflammatory effects even if it is used by the patient only for rescue purposes. A treatment for patients suffering from respiratory disease, particularly asthma (including allergic conditions, e.g. episodic or intermittent asthma), will therefore be to use the combination formoterol/budesonide for maintenance therapy as well as on an as needed basis (for rescue purposes), e.g. for prevention of exercise and/or allergen induced asthma.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Formoterol is a compound which can exist in several stereochemical forms. The present invention includes the individual stereoisomers as well as mixtures thereof. It is intended that the present invention includes geometrical isomers, rotational isomers, racemates, diastereomers and enantiomers, in particular the R,R enantiomer of formoterol.

[0014] Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids such as the hydrochloride, hydrobromide, sulfate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxy-naphthalene-carboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of this salt.

[0015] The present invention also encompasses compositions comprising the 22R epimer of budesonide as the second active ingredient.

[0016] A suitable unit dose of formoterol (as fumarate dihydrate) is in the range of from 1 μg to 48 μg, preferably from 2 μg to 24 μg, and more preferably between 3 μg and 12 μg. The daily dose of formoterol (as fumarate dihydrate), including maintenance therapy, should be in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, and more preferably from 3 μg to of 48 μg.

[0017] A suitable unit dose of budesonide is in the range of from 20 μg to 1600 μg, suitably from 30 μg to 800 μg, preferably from 50 μg to 400 μg, and more preferably between 100 μg and 200 μg. The daily dose of budesonide, including maintenance therapy, should be in the range of 20 μg to 4800 μg, preferably from 30 μg to 3200 μg, and more preferably from 40 μg to 1600 μg. The particular dose regimen will depend on the patient (age, sex, weight etc.) and the severity of the disease (mild, moderate, severe asthma etc.).

[0018] The molar ratio of the first active ingredient (as formoterol) to the second active ingredient of the invention, suitably lies in the range of from 1:1 to 1:100, preferably from 1:1 to 1:70, and more preferably from 1:1 to 1:50.

[0019] Preferably the mixture comprises one or more pharmaceutically acceptable additives, diluents or carriers, more preferably in an amount of from 50 μg to 4000 μg in each dose, most preferably in an amount of from 100 μg to 2000 μg and most preferably from 100 μg to 1000 μg. Examples of suitable additives, diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, and more preferably as the monohydrate.

[0020] One or more of the ingredients of the mixture may be in the form of dry powder, more preferably a small particle dry powder, most preferably an agglomerated small particle dry powder. Alternatively one or more of the active ingredients (a) or (b) are in the form of an ordered mixture with diluent, additive or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is preferably less than 10 μm.

[0021] Administration may be by inhalation orally or intranasally. The ingredients of the system are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler, or a nebulizer.

[0022] When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in a small particle form. They are dissolved, or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluorocarbons. Especially preferred propellants are P134a (tetrafluoroethane), P152a (difluoroethane) and P227 (heptafluropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an antioxidant and/or a stabilizing agent

[0023] When the ingredients of the system of the invention are adapted to be administered via a nebulizer they may be in the form of a nebulized aqueous suspension or solution, with or without suitable pH or tonicity

adjustment, either as a unit dose or multidose formulation.

EXAMPLES

[0024] The ingredients can be formulated as illustrated by the following examples which are not intended to limit the scope of the invention.

[0025] In the examples micronization is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler® is a trademark of Astra AB.

EXAMPLE 1

[0026] 4.5 Parts by weight of formoterol fumarate dihydrate were mixed with 915 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 2

[0027] 9 Parts by weight of formoterol fumarate dihydrate were mixed with 831 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronized bude-sonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 3

[0028] 6 Parts by weight of formoterol fumarate dihydrate were mixed with 894 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616, 100 Parts by weight of micronized bude-sonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 4

[0029] 12 Parts by weight of formoterol fumarate dihydrate were mixed with 788 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill, The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 5

[0030] A patient on maintenance treatment with the fixed combination formoterol fumarate dihydrate/budesonide in a dose of 4.5/80 μg or 4.5/160 μg bid additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks, with a maximum daily dose of 36/640 μg (8 puffs of 4.5/80 μg) and 36/1280 μg (8 puffs of 4.5/160 μg), respectively.

EXAMPLE 6

[0031] A patient with intermittent asthma uses the fixed combination formoterol fumarate dihydrate/budesonide as sole medication to be taken as needed until the asthma resolves. The highest recommended daily dose will be either 36/640 μg (8 puffs of 4.5/80 μg) or 36/1280 μg (8 puffs of 4.5/160 μg) for a period not exceeding 8-120 weeks. If symptoms still persist after that period of time - regular maintenance therapy should be considered.

Claims

1. Use of a composition comprising, in admixture

   (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
   (b) a second active ingredient which is budesonide;

   for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma **characterised in that** the use is for symptomatic relief, when needed, in addition to treating chronic asthma on a regular basis.

2. Use according to claim 1 wherein the composition is used for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma.

3. Use according to claim 1 wherein the composition is used for the manufacture of a medicament for use in the prevention or treatment intermittent asthma.

4. Use according to claim 1 wherein the composition is

used for the manufacture of a medicament for use in the prevention or treatment of episodes in chronic asthma.

5. Use according to any one of claims 1 to 4, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100, preferably from 1:1 to 1:70.

6. Use according to any one of claims 1 to 5, wherein the first active ingredient is formoterol fumarate dihydrate.

7. Use according to any previous claim, wherein the first active ingredient is the R,R enantiomer of formoterol.

8. Use according to any previous claim, wherein a unit dose of formoterol lies in the range of from 1 μg to 48 μg, preferably between 3 μg to 12 μg, calculated as formoterol fumarate dihydrate.

9. Use according to any previous claim, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, calculated as formoterol fumarate dihydrate.

10. Use according to any previous claim, wherein the second active ingredient is the 22R epimer of budesonide.

11. Use according to any previous claims, wherein a unit dose of budesonide lies in the range of from 20 μg to 1600 μg, preferably between 50 μg to 400 μg.

12. Use according to any previous claim, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 μg to 4800 μg, preferably from 30 μg to 3200 μg.

13. Use according to any previous claim wherein one or more of the ingredients is in the form of a dry powder.

14. Use according to any one of claims 1 to 12 wherein the composition is administered from a pressurised metered dose inhaler.

15. Use according to any previous claim, wherein the particle size of the active ingredients (a) and (b) is less than 10 μm.

16. Use according to any previous claims, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

17. Use according to claim 13, 15 or 16, wherein the pharmaceutically acceptable additive, diluent or carrier is lactose monohydrate.

18. Use according to claim 14, 15 or 16 wherein the ingredients are suspended in a liquid propellant mixture

19. Use according to claim 18 wherein the liquid propellant is P134a, P152a or P227 or mixtures thereof.

20. Use according to claim 18 wherein the liquid propellant is P227.

Patentansprüche

1. Verwendung einer Zusammensetzung enthaltend, als Mischung,

   (a) einen ersten Wirkstoff, bei dem es sich um Formoterol, ein pharmazeutisch annehmbares Salz oder Solvat davon oder ein Solvat eines solchen Salzes handelt; und
   (b) einen zweiten Wirkstoff, bei dem es sich um Budesonid handelt;

   zur Herstellung eines Medikaments zur Verwendung bei der Prävention oder Behandlung eines akuten Zustands an Asthma und/oder intermittierendem Asthma und/oder Episoden bei chronischem Asthma, **dadurch gekennzeichnet, daß** die Verwendung zur Linderung von Symptomen erfolgt, wenn erforderlich, zusätzlich zur Behandlung von chronischem Asthma auf regulärer Basis.

2. Verwendung nach Anspruch 1, wobei die Zusammensetzung zur Herstellung eines Medikaments zur Verwendung bei der Prävention oder Behandlung eines akuten Zustands von Asthma verwendet wird.

3. Verwendung nach Anspruch 1, wobei die Zusammensetzung zur Herstellung eines Medikaments zur Verwendung bei der Prävention oder Behandlung von intermittierendem Asthma verwendet wird.

4. Verwendung nach Anspruch 1, wobei die Zusammensetzung zur Herstellung eines Medikaments zur Verwendung bei der Prävention oder Behandlung von Episoden bei chronischem Asthma verwendet wird.

5. Verwendung nach einem der Ansprüche 1 bis 4, wobei das Molverhältnis von (a) zu (b), berechnet als Formoterol:Budesonid, 1:1 bis 1:100, vorzugsweise 1:1 bis 1:70, beträgt.

6. Verwendung nach einem der Ansprüche 1 bis 5, wobei es sich bei dem ersten Wirkstoff um Formoterol-

fumarat-dihydrat handelt.

7. Verwendung nach einem der vorherigen Ansprüche, wobei es sich bei dem ersten Wirkstoff um das R,R-Enantiomer von Formoterol handelt.

8. Verwendung nach einem der vorherigen Ansprüche, wobei eine Einheitsdosis von Formoterol im Bereich von 1 μg bis 48 μg, vorzugsweise zwischen 3 μg und 12 μg, liegt, berechnet als Formoterolfumarat-dihydrat.

9. Verwendung nach einem der vorherigen Ansprüche, wobei die Tagesdosis an Formoterol, einschließlich Erhaltungstherapie, im Bereich von 1 μg bis 100 μg, vorzugsweise von 2 μg bis 60 μg, liegt, berechnet als Formoterolfumarat-dihydrat.

10. Verwendung nach einem der vorherigen Ansprüche, wobei es sich bei dem zweiten Wirkstoff um das 22R-Epimer von Budesonid handelt.

11. Verwendung nach einem der vorherigen Ansprüche, wobei eine Einheitsdosis von Budesonid im Bereich von 20 μg bis 1600 μg, vorzugsweise zwischen 50 μg und 400 μg, liegt.

12. Verwendung nach einem der vorherigen Ansprüche, wobei die Tagesdosis an Budesonid, einschließlich Erhaltungstherapie, im Bereich von 20 μg bis 4800 μg, vorzugsweise von 30 μg bis 3200 μg, liegt.

13. Verwendung nach einem der vorhergehenden Ansprüche, wobei einer oder mehrere der Wirkstoffe in Form eines Trockenpulvers vorliegt.

14. Verwendung nach Ansprüche 1 bis 12, wobei die Zusammensetzung aus einem unter Druck stehenden Inhalationsgerät für eine dosierte Verabreichung (Pressurised Metered Dose Inhaler) verabreicht wird.

15. Verwendung nach einem der vorhergehenden Ansprüche, wobei die Teilchengröße der Wirkstoffe (a) und (b) unter 10 μm liegt.

16. Verwendung nach einem der vorhergehenden Ansprüche, wobei die Zusammensetzung zusätzlich einen oder mehrere pharmazeutisch annehmbare Zusatzstoffe, Verdünnungsmittel oder Träger enthält.

17. Verwendung nach Anspruch 13, 15 oder 16, wobei es sich bei dem pharmazeutisch annehmbaren Zusatzstoff, Verdünnungsmittel oder Träger um Laktosemonohydrat handelt.

18. Verwendung nach Anspruch 14, 15 oder 16, wobei die Inhaltsstoffe in einer flüssigen Treibmittelmischung suspendiert sind.

19. Verwendung nach Anspruch 18, wobei es sich bei dem flüssigen Treibmittel um P134a, P152a oder P227 oder Mischungen davon handelt.

20. Verwendung nach Anspruch 18, wobei es sich bei dem flüssigen Treibmittel um P227 handelt.

Revendications

1. Utilisation d'une composition comprenant, en mélange :

   (a) un premier principe actif qui est le formotérol, un sel ou solvate pharmaceutiquement acceptable de celui-ci ou un solvate d'un tel sel ; et
   (b) un deuxième principe actif qui est le budésonide ;

   pour la fabrication d'un médicament destiné à être utilisé pour la prévention ou le traitement d'un état aigu d'asthme et/ou de l'asthme intermittent et/ou d'épisodes d'asthme chronique, **caractérisée en ce que** l'utilisation est destinée au soulagement symptomatique, lorsque cela est nécessaire, en plus du traitement régulier de l'asthme chronique.

2. Utilisation selon la revendication 1, selon laquelle la composition est utilisée pour la fabrication d'un médicament destiné à être utilisé pour la prévention ou le traitement d'un état aigu d'asthme.

3. Utilisation selon la revendication 1, selon laquelle la composition est utilisée pour la fabrication d'un médicament destiné à être utilisé pour la prévention ou le traitement de l'asthme intermittent.

4. Utilisation selon la revendication 1, selon laquelle la composition est utilisée pour la fabrication d'un médicament destiné à être utilisé pour la prévention ou le traitement d'épisodes d'asthme chronique.

5. Utilisation selon l'une quelconque des revendications 1 à 4, selon laquelle le rapport molaire de (a) à (b) calculé en termes de formotérol sur budésonide, va de 1:1 à 1:100, de préférence de 1:1 à 1:70.

6. Utilisation selon l'une quelconque des revendications 1 à 5, selon laquelle le premier principe actif est le fumarate de formotérol dihydraté.

7. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle le premier principe actif est l'énantiomère R,R du formotérol.

8. Utilisation selon l'une quelconque des revendica-

tions précédentes, selon laquelle une dose unitaire de formotérol se situe dans la gamme allant de 1 µg à 48 µg, de préférence de 3 µg à 12 µg, calculée en termes de fumarate de formotérol dihydraté.

9. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle la dose journalière de formotérol, y compris la thérapie d'entretien, se situe dans la gamme allant de 1 µg à 100 µg, de préférence de 2 µg à 60 µg, calculée en termes de fumarate de formotérol dihydraté.

10. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle le deuxième principe actif est l'épimère 22R du budésonide.

11. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle une dose unitaire de budésonide se situe dans la gamme allant de 20 µg à 1600 µg, de préférence de 50 µg à 400 µg.

12. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle la dose journalière de budésonide, y compris la thérapie d'entretien, se situe dans la gamme allant de 20 µg à 4800 µg, de préférence de 30 µg à 3200 µg.

13. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle un ou plusieurs des principes sont sous forme de poudre sèche.

14. Utilisation selon l'une quelconque des revendications 1 à 12, selon laquelle la composition est administrée à partir d'un inhalateur doseur sous pression.

15. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle la taille de particules des principes actifs (a) et (b) est inférieure à 10 µm.

16. Utilisation selon l'une quelconque des revendications précédentes, selon laquelle la composition comprend en outre un ou plusieurs additifs, diluants ou supports pharmaceutiquement acceptables.

17. Utilisation selon la revendication 13, 15 ou 16, selon laquelle l'additif, le diluant ou le support pharmaceutiquement acceptable est le lactose monohydraté.

18. Utilisation selon la revendication 14, 15 ou 16, selon laquelle les principes sont mis en suspension dans un mélange de propulseur liquide.

19. Utilisation selon la revendication 18, selon laquelle le propulseur liquide est P134a, P152a ou P227 ou des mélanges de ceux-ci.

20. Utilisation selon la revendication 18, selon laquelle le propulseur liquide est P227.

REFERENCES CITED IN THE DESCRIPTION

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- EP 717616 A **[0026] [0027] [0028] [0029]**
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